REMARKS

Claim 2 has been amended to correct a typographical error. No new matter has been added. Therefore, entry of the amendment is respectfully requested.

DOUBLE PATENTING REJECTION UNDER 35 U.S.C. §101

Claims 1-21 have been provisionally rejected under §101 as claiming the same invention as that of claims 1-21 of copending Application no. 10/759,293, all of which are allegedly directed to a method treating leukemia by administering 0.15 mg/kg ATO of the patient's body weight for a maximum of 60 days. Applicants respectfully traverse the rejection because the same inventions are not being claimed.

First, none of the claims is directed to a method. Claim 1 of the '293 application is directed to a kit, comprising arsenic trioxide and instructions for the administration of said arsenic trioxide to a patient diagnosed with acute promyelocytic leukemia, comprising delivering a therapeutically effective dosage amount of about 0.15 mg/kg of said arsenic trioxide, wherein said amount is based on the weight of the patient.

On the other hand, Claim 1 of the present application is directed to a kit, comprising arsenic trioxide and instructions for the administration of said arsenic trioxide to a patient diagnosed with acute promyelocytic leukemia, comprising delivering a therapeutically effective dosage amount of about 0.15 mg/kg of said arsenic trioxide *once a day*.

The respective claims differ at least in terms of the instructions regarding the frequency with which the ATO is delivered, *i.e.*, the claims of the '293 application reciting delivery once a day. Therefore, there is no basis for double patenting under the statute. Accordingly, reconsideration and withdrawal of the rejection are requested.

REJECTION UNDER 35 U.S.C. §103

Claims 1-21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,720,011 to Zhang ("*Zhang*"), or Chinese Patent No. 1,061,908 to Yang, *et al* ("*Yang*"), or Chen, *et al.*, Blood *88(3)*:1052-61 (1996) ("*Chen*"). The Examiner has stated that each of the three cited publications teaches a method of treating leukemia comprising administering arsenic trioxide (ATO) to a patient. The Examiner has acknowledged that the prior art does not teach the instant amounts or dosages of ATO. However, the Examiner has determined that it would have been obvious to one having ordinary skill in the art to determine the optimum amount and number of doses of ATO, and that one would have motivated to do this in order to develop a method that would have been most effective in treating leukemia, and further that one of ordinary skill in the art would have been expected to put ATO in some sort of package or kit for storage purposes.

Applicants respectfully traverse the rejection because the cited publications would not have established *prima facie* obviousness, regardless of whether they were considered separately or collectively. Assuming *arguendo* that the cited publications would have established *prima facie* obviousness, Applicants submit that the claimed invention achieves an unexpected result, particularly when the claimed invention is viewed from the standpoint of the prior art in its entirety.

ARGUMENT

Introduction

The claims of U.S. Patent 6,723,351, which issued from the parent application, were allowed over the publications that have been cited against the claims of the present application. Thus, arguments and evidence presented in the parent application have been repeated herein. Claims 1-21 of the present application are directed to kits comprising arsenic trioxide and

instructions for, *inter alia*, administration of said arsenic trioxide to a patient diagnosed with APL, comprising delivering a therapeutically effective dosage amount of about 0.15 mg/kg of arsenic trioxide to said patient once per day. This is in contrast to what is known in the art as "flat dosing", *i.e.*, a regimen wherein all patients receive the same amount of drug. An effective weight-based dosing methodology for treatment of APL is nowhere to be found in the prior art. Nothing in the prior art implicates, let alone teaches, that it is possible -- safely and effectively -- to dose an APL patient with arsenic trioxide, based upon the patient's weight. More particularly, no reference teaches nor does any combination suggest the use of a patient's weight to determine the dose of arsenic trioxide in order to treat a patient with APL.

In support of its position that the presently claimed invention is non-obvious, and thus patentable over the prior art, Applicants are providing the Examiner with a copy of a declaration under Rule 132 by Ralph Ellison, M.D., that was submitted in connection with the parent application. As pointed out in the declaration, Dr. Ellison was instrumental in the clinical development of TRISENOX®, an intravenous arsenic trioxide (ATO) product that has been approved by the FDA. Dr. Ellison also explains that in contrast to non-cancerous diseases, the standard approach to dosing anti-cancer drugs is *not* based on patient weight. More specifically, weight-based dosing is not standard in oncology, let alone APL. (See Ellison Declaration, ¶¶2-6).) In fact, even after a comprehensive search, Applicants' attorneys have not identified one approved use of a cancer drug for delivery on a weight basis. The teachings of the cited prior art are entirely supportive of and consistent with this position.

The Cited Prior Art

Yang's invention is directed to a method for the preparation of a type of medication that contains arsenic for the treatment of early cervical and skin cancer. There is no disclosure of treating leukemias such as APL. In addition, there is no disclosure of treating APL patients with a dosage of about 0.15 mg/kg of ATO once per day.

According to the disclosure of this patent publication, the primary raw materials in the medication are white arsenic, alunite, realgar, and *Commiphora Myrrha*, with each being present in the medication not only in terms of specific amounts, but specific weight ratios, *i.e.*, 3:4 for the white arsenic and alunite, and 1:2 for the realgar and *Commiphora Myrrha*, and optimum percentages by weight of 18% for the arsenic trioxide and 6% for the aluminum arsenate. On page 6, *Yang* teaches that in order to prepare the medication, each ingredient is pre-pulverized and weighed in accordance with the following weight ratios: White arsenic 30-75; alunite 40-100; realgar 2-8; and *Commiphora Myrrha* 1-4. On page 7, *Yang* teaches even that even better results can be obtained when the ingredients are added in specific weight ratios of 3-4 for the white arsenic and alunite; and a weight ratio of 2:1 for the realgar, and *Commiphora Myrrha*.

On page 8, *Yang* teaches that the medication may be formulated into tablets, bougie, and other formulations using conventional methods. On pages 9-10, *Yang* provides a summary of a study of clinical treatment of 230 patients with early cervical cancer. There is no disclosure, however, as to how these patients were dosed with the medication. Thus, aside from the fact that this publication is directed to treatment of a different cancer than APL, there is no disclosure or suggestion to treat APL patients with about 0.15 mg/kg of ATO once per day.

Chen reports on *in vitro* studies conducted in order to elucidate the possible cellular and molecular mechanisms of arsenic trioxide on APL patients. In the second paragraph of this publication, *Chen* refers to a report conducted in China showing that administration of 10 mg per day of arsenic trioxide via intravenous infusion for 28-60 days induced clinical complete remission in 65.6% of APL patients, and that 28.2% of patients had a survival of more than ten years. Thus, *Chen* teaches a method of treating APL based on flat dosing of ATO. Once again, each patient was dosed with an identical amount of drug. In the last full paragraph on page 1053, *Chen* makes additional reference to another clinical use of arsenic trioxide in connection with relapsed APL patients, wherein the drug was administered to eight relapsed APL patients at a dose of 10 mg/day via intravenous drip diluted in 500 mL of 5% glucose saline and administered within two hours. Here again, all eight patients received identical amounts of drug regardless of their weight.

The invention disclosed in *Zhang* is directed to an intravenous pharmaceutical composition for the treatment of cancers, particularly types of leukemia such as APL and acute myeloid leukemia (AML), with a composition comprising ATO, sodium chloride, and water, and more particularly a composition containing 1 g - 10 g ATO, 8 g of sodium chloride and 1000 mL of sterile water. See, col. 1, lines 33-35 and 41-46. The only disclosure in *Zhang* regarding the actual dosage amount to administer to a patient may be found on column 2, lines 9-11 and 14-16, wherein *Zhang* teaches that an effective daily dose for an adult has been found to be 10 mL of a composition containing 10 g/L of ATO added to 500 mL of a 10% glucose solution, and that the amount of the composition used should be adjusted based on the concentration of the arsenic trioxide in the composition. Accordingly, *Zhang* teaches a *single* flat dose of 10 mL of a

particular composition. Ten milliliters of a composition containing 10 g of arsenic trioxide in 500 mL of solution equates to the 10 mg flat dose, and thus is consistent with the other cited publications such as *Chen*. The disclosure in lines 14-16 indicates that more of less of *Zhang's* composition would be administered in order to achieve a flat dosage of 10 mg.

In the "EXAMPLE" on columns 2-3, *Zhang* summarizes treatment of 110 subjects diagnosed with APL, ranging from 13 to 65 years old (*Zhang*, col. 2, lines 60-62), and thus included both children and adults. Treatment entailed administration of the "composition of the invention for 2-4 weeks". Col. 3, lines 6-7. Notwithstanding the statement on col. 2, lines 16-17 (*i.e.*, that the appropriate dose should be decreased accordingly for children), the EXAMPLE contains no mention of administering a decreased dose of the ATO composition to the children who were treated.

In view of the foregoing, Applicants respectfully submit that *Zhang* would not have motivated one skilled in the art to treat an APL patient with about 0.15 mg/kg of ATO once per day, or produce the claimed kits. Thus, *Zhang* adds nothing over and above the 10 mg flat dose reflected elsewhere in the prior art of record. In fact, it was not until after Applicants' priority date, with the publication by Zhang, *et al.*, Modern Pathology *13*:954-61 (2000) (PTO-1449, page 4, CR2), that the use of weight-based dosing was even contemplated.

Discussion of other prior art of record

Soignet, *et al.*, Blood *88(10)*: 219A (1996)(PTO-1449, page 4, CV2), relates to an initial evaluation of melarsoprol, an organic arsenical, for treating cancer in four patients, to whom the drug was administered on a weight basis. *Soignet* indicates that it was too early to evaluate any of the four patients for response. There is no disclosure or suggestion to use *arsenic trioxide* on a weight basis. In fact, *Soignet* teaches that

melarsoprol may be preferred over arsenic trioxide, in terms of broader activity. If anything, therefore, this publication teaches away from the claimed invention.

U.S. Publication no. 20020183385 ("the '385 application") to Ellison, *et al.* (PTO-1449, page 1, AF) teaches treating a variety of cancers, including solid tumors, with arsenic trioxide. Paragraph 73 of the '385 application, directed to dosage amounts, lists the weight of a patient as one of many dosage-determining factors, the others being the severity of the condition to be treated, the route of administration, and the age, condition and response of the individual patient.

Inasmuch as this disclosure is boilerplate in the pharmaceutical patent literature, the fact remains that approved anticancer drugs are dosed on the basis of body surface area, as Dr. Ellison attested in his declaration. Moreover, the remainder of the above-noted paragraph describes ranges of dosage amounts with absolutely no basis in weight: "[I]n general, the total daily dose ranges for the conditions described herein are generally from about 10 mg to about 200 mg administered in divided doses administered parenterally or orally or topically. A preferred total daily dose is from about 0.5 mg to about 70 mg of the active ingredient." Thus, the skilled artisan would not have been motivated to produce a kit for treating APL that contains ATO and instructions for administering ATO in a dosage of about 0.15 mg/kg once per day, with a reasonable expectation that such treatment using the kit would be both effective and safe.

The Westervelt abstract (PTO-1449, page 4, CU2) reports the results of treatment of a single patient with two different flat doses. More specifically, Westervelt, *et al.* first treated this patient with a flat dose of 10 mg per day. That dosage proved ineffective, however, and Westervelt, *et al.* moved to a 50 mg flat dose, which they found to be toxic. They concluded that

significant work in Phase I/II studies would be necessary to identify a proper dosing scheme for arsenic trioxide in APL; hence, no dosing approach was recommended.

The Westervelt abstract describes the dosages of ATO in terms of flat doses, *i.e.*, "10 mg/day" and "50 mg/day". It also makes parenthetical reference to the same dosages in weight-based terms, namely "(0.08 mg/kg/day)" and "(0.4 mg/kg/day)" respectively. At first blush, this disclosure raises the possibility of whether the patient was actually dosed on a weight basis. This was not the case, however. The patient identified in the Westervelt abstract was the first of 5 patients involved in a study, the complete results of which are disclosed in Zhang, *et al.*, Modern Pathology *13*:954-61 (2000). Westervelt is a co-author of the Zhang publication. On the right column on page 956, *Zhang* explains that the first patient was administered a flat dose of ATO:

> Patient 1 was started As_2O_3 at 10 mg daily (0.08 mg/kg/day) for the first 11 days and 50 mg daily (0.4 mg/kg/day) for the additional 17 days, and the total As_2O_3 administered was 550 mg. The remaining four patients were based on actual body weight, starting at 0.1 mg/kg/day (Table 2).

(Emphasis added.) *Zhang*, of course, is not prior art. At the same time, though, it is clear from *Zhang* that the teachings of the Westervelt, *et al.* abstract would not have rendered the presently claimed invention obvious. See also, ¶ 7 of the Ellison declaration.

On the other hand, Westervelt, *et al.* is believed to establish that at the time that the claimed invention was made, determining dosage schemes for treatment of APL with ATO was unpredictable. After concluding that treatments of a patient with flat doses of 10 mg and 50 mg were unsuccessful,

Westervelt, *et al.* caution that, "despite its therapeutic potential for APML, intravenous arsenic trioxide is not without significant toxicity, especially at escalated doses which may be required to achieve responses in highly resistant disease." Thus, Westervelt, *et al.* advocate use of ATO "with caution only in the absence of other viable treatment options, until optimum dosing parameters can be established in phase I/II clinical trials."

In conclusion, Applicants respectfully submit that the collective teachings of the prior art would not have established *prima facie* obviousness, as there is no suggestion or motivation to produce a kit for treating APL that contains ATO and instructions for administering ATO in a dosage of about 0.15 mg/kg once per day, with a reasonable expectation that the treatment using the claimed kit would have been effective and safe.

Genesis of the Present Invention

As described in the present specification beginning on page 29, in the course of developing a clinical protocol for treatment of APL with ATO, the present inventors also initially adopted a flat-dosing approach. For their first five patients, they used a daily 10-mg dose. Patient 5 in the initial group relapsed within 24 days of achieving total remission and before completion of the consolidation therapy. As the patient was a very large individual (163 kg), the inventors questioned whether he might have received too little drug at a flat dose of 10 mg daily. The relevant literature did not suggest this problem, since there was no teaching that the size of a patient should be considered in arriving at an appropriate dosage. See also, ¶ 8 of the Ellison declaration.

Since the drug had been well tolerated by the initial patients, and in order to avoid the possibility of under dosing, as was believed to have occurred with Patient 5, the dose was

increased to a 15 mg flat dose for all subsequent patients. This dosage amount was given to Patients 6 and 7. Patient 8 was a 13 year-old girl and was of smaller stature, however. For this patient, therefore, the inventors chose to revert to the original, 10 mg-daily dose, as a precaution against the possibility of overdosing. Patient 9 was a 9 year-old boy and, because of his size, was given a flat dose of only 5 mg daily. Patient 10 was given the newer dosage of 15 mg daily. See also, Table 3 on page 41 of the present specification, and ¶9 of the Ellison declaration.

Upon reviewing the results for the first ten patients, the inventors concluded that the standard flat dosing method seemed not to be efficacious for large people and yet was too toxic for small people. They also concluded that their initial approach of adjusting the flat dose was arbitrary and did not allow for a balancing of toxicity and efficacy in a treatment protocol to be used across a broad population of patients. Prior to treating Patient 11, therefore, the inventors decided to implement a technique other than flat dosing. Rather than turning to standard BSA (body surface area), the technique widely used by oncologists for dosing of chemotherapeutic drugs, the inventors chose to attempt to develop a weight-based dosing scheme. Employing data generated from the first ten patients, the inventors calculated a putative weight-based dose of 0.15 mg/kg daily. This dose was used for the next two patients and was ultimately chosen to complete the study (see Table 3 on page 41). It was also the dose used to conduct the pivotal phase III trial in which a total of 40 patients participated. The results of this trial are reported in Soignet, *et al.*, J. Clin. Oncology *19*:3852-3860 (2001) (PTO-1449, page 4, CT2). *Soignet, et al.* report that arsenic trioxide treatment is both safe and effective. Eighty-five (85) percent of patients achieved

clinical complete remission, and there were no treatment-related deaths.

Unexpected Results

Applicants submit that even if *prima facie* obviousness could have been established, both the Ellison Declaration and third-party statements in various post-filing publications convincingly refute any *prima facie* case of obviousness.

Post-filing reports by third parties evidence a persisting concern over toxicity, even in connection with the weight-based dosing regimens that were under evaluation by then.

For example, the Westervelt group reported the results of another of its studies to determine, in the context of treating relapsed or refractory APL, the maximum tolerated dose or the minimum effective dose of ATO, thereby further to illuminate efficacy at that dose and to delineate the acute and chronic toxicities of ATO. Westervelt, *et al.*, Blood *98(2)*:266-71 (2001)(PTO-1449, page 4, CS2). Once again, the study design entailed a weight-based dosing scheme, this time beginning at a dose of 0.10 mg/kg and increasing in increments of 0.05 mg/kg per day (page 267, left column). The study was curtailed at 0.10 mg/kg per day, however, on account of three unexplained deaths, which the investigators suspected were due to arsenic-related cardiac arrhythmia. The (2001) Westervelt publication concludes with a warning to the effect that the deaths suggest more toxicity, associated with the ATO dosages, than had been recognized previously, and that until these issues were better defined, ATO should be used with caution.

Westervelt, *et al.* concede that their results were in direct contrast with the results achieved in the trial reported in Soignet, *et al.* (2001) (*supra*) from the standpoint of the unexplained deaths. On the right column of page 270, they acknowledge that in the studies reported in *Soignet*, 52 patients

were treated without any treatment-related deaths. While proffering various theories to explain the differing results, Westervelt, *et al.* reached no conclusions on this point.

From the viewpoint of *Soignet* (2001), the 3 unexplained deaths reported in *Westervelt* (2001) were simply an anomaly: "Recently, other investigators have reported episodes of nonsustained ventricular tachycardia in patients being treated with ATO for relapsed APL. Ventricular arrhythmias, other than the episode of torsades discussed above, were not observed in patients on this study, and these events have not been reported by Chinese investigators with clinical experience in using ATO." (page 3859; citations omitted). Applicants submit that *the skilled artisan* would have deemed the results of use of Applicants' claimed kits as unexpectedly effective, without the toxicities observed by Westervelt's group.

Overall, the results achieved to date in connection with Applicants' claimed invention are in sharp contrast to the state of the art. For example, in paragraph 11 of his declaration, Dr. Ellison states that since the time of FDA approval for ATO (Trisenox®), data already in the literature have been augmented by the results of treating an additional 2,228 patients with doses of about 0.15 mg/kg per day or greater. To date, these additional results have included no reported deaths attributed to cardiac arrhythmia.

Lastly, as described in ¶12 of his declaration, Dr. Ellison explains that subsequent to the present invention, another group of oncologists chose to modify flat dosing to a dosing based upon the patient's size; this, in recognition of a need to protect patients from toxic doses of ATO during the APL treatment. See Au, *et al.*, Annals of Oncology *14*:752-57 (2003) (copy enclosed). Au *et al.* adopted a BSA dosing scheme, however. Thus, they described the use of BSA dosing in the context of treating a group of patient with relapsed APL.

Initial treatment was on a flat-dosage basis for APL patients who underwent bone-marrow transplantation and ATO therapy. For double-relapse patients, however, the dosage was metered to take into account the size of the patient on a surface area basis. The difference in initial dosing and double-relapse dosing can only be interpreted as an acknowledgement of the need to balance toxicity and efficacy for the patients who had been weakened by extensive therapy beforehand. When faced with the same problem that the present inventors confronted, in other words, Au, *et al.* resorted to more conventional treatment scheme, with dosing based upon patient surface area.

Conclusion

In view of the foregoing, Applicants submit that the collective teachings of the prior art would not have rendered the claimed invention obvious. The only way in which a case of *prima facie* obviousness could be established is via impermissible hindsight reconstruction. Even if the prior art did establish *prima facie* obviousness, the unexpected results of the claimed invention from the standpoints of efficacy and safety weigh in favor of patentability.

REJECTIONS BASED ON OBVIOUSNESS-TYPE DOUBLE PATENTING

The claims have been rejected on the ground of provisional obviousness-type double patenting over claims of various of Applicants' other continuation applications. As discussed with the Examiner, Applicants are submitting a terminal disclaimer that names all of Applicants' 16 other applications filed on January 16, 2004, all of which entail dosing of ATO on a weight basis, simply in order to expedite prosecution.

As also discussed with the Examiner, Applicants are submitting herewith a terminal disclaimer over U.S. Patent 6,723,351, also to expedite prosecution.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: August 31, 2004

Respectfully submitted,

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